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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 04/08/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/690,647

Applicant(s)

GREENBURG

Examiner

Mary M. Schmidt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 18 is/are allowed.
- 6) ☒ Claim(s) 1,3-17 and 19-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 2-19-03 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____ :
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. The restriction requirement mailed 12/17/02 is no longer required. Claims 1 and 3-28 are pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

3. Claims 1, 3-14 and 19-28 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 3-14 are drawn broadly to inhibitors of any ERK1 or ERK2 or a JNK gene or protein to reduce lipolysis, and which would thereby prevent or treat a disease or condition in a subject that was caused by lipolysis or elevated FFA levels in the subject. New claims 19-28 further specify the method of claim 1, wherein the inhibitor is a dominant negative mutant of ERK1/2, a MEK and/or a JNK; wherein the subject is overweight or obese; wherein the disease or condition is caused, or contributed to, by TNF-alpha induced lipolysis; wherein the disease or condition is caused, or contributed to, by basal lipolysis; wherein the inhibitor does not interact with a PPAR-gamma receptor and the inhibitor is not sodium salicylate; wherein the inhibitor is

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selected from the group consisting of an antisense, a triplex molecule, a ribozyme and a dominant negative mutant targeted to ERK1/2 or a MEK; further comprising determining the level of activity of ERK1/2 or a MEK in the subject; wherein the level of activity of ERK1/2 or a MEK is determined in a sample of fat cells from the subject; wherein the subject is administered in the presence of a carrier that facilitates entry of the inhibitor into cells of the subject; wherein the inhibitor is administered locally.

There are many possible compositions which could be considered an inhibitor of ERK1/2, a MEK or a JNK in any whole organism as broadly claimed. The claimed compositions are further limited to their ability to reduce lipolysis in the subject. Neither the art nor the specification as filed teaches a representative number of such compositions which specifically have the ability to inhibit lipolysis.

The specification teaches by way of example sodium salicylate, BRL (after pre-treatment) and PGJ2 (after pre-treatment) in 3T3-L1 adipocytes reduces TNF-alpha induced lipolysis (where ERK1 / 2 activation is increased), the MAP kinase inhibitor PD98059 reduces TNF-alpha induced lipolysis in human cells in cell culture, and in contrast, the p38 kinase inhibitor SB203580 stimulates TNF-alpha induced lipolysis. The specification teaches only prophetically design of other MAPK inhibitors. Although there are some general MAPK inhibitors known in the art, neither the specification nor the art teach design of specific inhibitors which would have the claimed functions *in vivo*. The examples of inhibitors taught by the specification for use in cells in culture for reduction of lipolysis in cell culture cells induced in a particular way, do not

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correlate broadly to any possible inhibitor of any MAPK pathway composition for the functions claimed in any whole organism. Applicant thus would not have been in possession of the scope of claimed inhibitors at the time the invention was made.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claims lack written description since the specification as filed has not disclosed a representative number of species from the genus of any possible ERK1/2, MEK or JNK gene or protein inhibitor from any species of whole organism subject such that one of skill in the art would have been able to readily envisage the representative number of species of such inhibitors

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having the claimed functions of prevention or treatment of any possible disease or condition in any whole organism caused by or contributed by lipolysis or elevated FFA levels in the whole organism subject. The claims are drawn to methods of treatment and compounds having the functional use for treatment, which require a knowledge of the described disease states which are treated upon administration of the claimed compounds. The invention thus rests on the correlation of a desired prevention or treatment function to the claimed and disclosed therapeutic or preventative compounds. The specification as filed, however, does not teach any specific identifying design characteristics of any ERK1/2, MEK or JNK gene or protein inhibitor having a clear inhibition of a specific ERK1/2, MEK or JNK in a whole organism environment such that the function of treating, or preventing any such disease caused by or contributed to by lipolysis or elevated FFA levels is achieved. The specification as filed provides a correlation between certain MAPK inhibitors and results in cells in cell culture, but does not provide a sufficient correlation as to the actual design of any possible specific ERK1/2, MEK or JNK preventative or therapeutic agent for administration to any subject for the treatment, or preventing of any disease related to lipolysis or elevated FFA levels as claimed. In the absence of a more specific description of the design criteria (ie., specific gene and/or protein ERK1/2, MEK or JNK sequences, modifications, routes of administration, formulation) needed to visualize antisense, ribozyme, triplex or other types of inhibitors of ERK1/2, MEK, or JNK effective for treatment, or preventing any disease caused by or contributed to by lipolysis or elevated FFA levels in a subject as claimed and a specific nexus to the therapeutic or preventative results achieved in a particular disease

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environment in a particular subject, one of skill in the art would not have sufficient written description of the claimed compounds. It was art recognized at the time the invention was made that specific features of drugs to target a specific biomolecule such as ERK1/2, MEK or JNK *in vivo*, and features which would deliver the molecule to the appropriate location in the whole organism, were not readily visualized in the art and not available to the skilled artisan based on knowledge of the target molecule name. Therefore, the specification as filed does not show that Applicants' were in possession of (the knowledge of) a representative number of the claimed inhibitors at the time the invention was made to teach possession of the invention having the claimed functional limitations for treatment or preventing the breath of claimed diseases in any subject.

Response to Arguments

4. Applicant's arguments filed 3/4/02 have been fully considered but they are not persuasive.

Applicant states that "there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed (Revised Interim Written Description Guidelines Training Materials). Applicant further submits that a person of skill in the art would recognize from the disclosure that Applicant was in possession of the claimed invention at the time the application was filed." Applicant states that "[a] representative number of ERK1/2 inhibitors are explicitly disclosed in the specification." However, applicant does not further point to the location in the specification where these inhibitors are disclosed. Applicant

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further states that the “specification describes numerous species of MAPK pathway inhibitors. In particular, the specification describes that an inhibitor of a kinase can be:

any molecule which decreases the activity of the kinase or decreases the protein level of the kinase. Thus, a kinase inhibitor can be a small molecule which decreases activity of the kinase, e.g., by interfering with interaction of the kinase with another molecule, e.g., its substrate. It can also be a small molecule which decreases expression of the gene encoding the kinase. An inhibitor can also be an antisense nucleic acid, a ribozyme, an antibody, a dominant negative mutant of the kinase, or a phosphatase. (From page 9, lines 18-23 of the specification)

However, this teaching does not further describe the claimed invention as amended to claim inhibitors of the ERK1/2, MEK or JNK genes or proteins from any possible species of organism since it only generally discusses kinases. As reiterated above, the MPEP requires that one of skill in the art be able to immediately visualize a representative number of species of the claimed inhibitors having a correlated function to prevention and/or treatment of diseases associated with lipolysis or elevated FFA levels in a subject. Since the specification as filed only teaches sodium salicylate, BRL (after pre-treatment) and PGJ2 (after pre-treatment) in 3T3-L1 adipocytes reduces TNF-alpha induced lipolysis (where ERK1 / 2 activation is increased), and that the MAP kinase inhibitor PD98059 reduces TNF-alpha induced lipolysis in human cells in cell culture, and since no structural correlation has been taught between these molecules and any other potential MEK, ERK1/2 or JNK inhibitors, one of skill in the art would not accept these examples as representative of the genus of inhibitors used for the claimed functions.

Applicant states that the “specification as filed elaborates on all of these inhibitors. In addition, as acknowledged by the Examiner, the specification discloses that several species of

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MAPK pathway inhibitors were reduced to practice. For example, the specification discloses that PD98059 and NaSal inhibit the MAPK pathway and inhibit lipolysis. Sufficient inhibitors are described that a person of skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. Applicant notes that the particular structure of the different inhibitors is not a necessary common attribute of the elements possessed by the members of the genus.”

However, according to the MPEP, description of a particular function is not a sufficient description of a composition (or in the instant case, a composition used in a method), unless one of skill in the art would be able to immediately envisage the structure from the description in the specification as filed. One of skill in the art has no basis in the specification as filed for understanding or envisaging the structure of the claimed inhibitors based on the names ERK1/2, MEK or JNK alone. Since compositions used as pharmaceuticals are organic molecules that have a particular chemistry and structure, one of skill in the art would not be in possession of the compound absent the defined characteristics of the compound. Furthermore, the instant compounds must have a particular associated function in a whole organism subject (*in vivo*). Due to the complexity of the environment of a whole organism subject, one of skill in the art can not readily envisage the chemical and physical structure of any ERK1/2, MEK, or JNK gene or protein inhibitor absent specific design criteria such as the organic chemical composition. In the case of an antisense molecule, the nucleic acid sequence of the molecule must be known that is

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complementary to the target ERK ½, MEK or JNK gene sequence, which differs from organism to organism.

Applicant further states that “antisense, ribozyme and other gene inhibitors can be designed and tested according to methods known in the art. Designing such molecules is considered conventional in the art, it is a routine-art-recognized technique. The level of skill in the art is high. Even if, e.g., certain antisense molecules are not functioning adequately, a person of skill in the art can find others that will without undue experimentation.”

As argued above, due to the complexity of the *in vivo*, whole organism subject, environment, one of skill in the art would not have been able to find specific nexus between any potential antisense, ribozyme, or small molecule chemical drug and its effects on the breath of diseases claimed. Hence, one of skill in the art would not have recognized that application was in possession of the breath of claimed methods using the claimed compounds at the time the invention was made.

5. Claims 1, 3-17 and 19-28 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. Claims 1 and 3-14 are drawn broadly to inhibitors of any ERK1 or ERK2 or a JNK gene or protein to reduce lipolysis, and thereby prevent or treat a disease or condition in a subject that

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was caused by lipolysis or elevated FFA levels in the subject. New claims 19-28 further specify the method of claim 1, wherein the inhibitor is a dominant negative mutant of ERK1/2, a MEK and/or a JNK; wherein the subject is overweight or obese; wherein the disease or condition is caused, or contributed to, by TNF-alpha induced lipolysis; wherein the disease or condition is caused, or contributed to, by basal lipolysis; wherein the inhibitor does not interact with a PPAR-gamma receptor and the inhibitor is not sodium salicylate; wherein the inhibitor is selected from the group consisting of an antisense, a triplex molecule, a ribozyme and a dominant negative mutant targeted to ERK1/2 or a MEK; further comprising determining the level of activity of ERK1/2 or a MEK in the subject; wherein the level of activity of ERK1/2 or a MEK is determined in a sample of fat cells from the subject; wherein the subject is administered in the presence of a carrier that facilitates entry of the inhibitor into cells of the subject; wherein the inhibitor is administered locally.

There are many possible compositions which could be considered an inhibitor of ERK1/2, a MEK or a JNK in any whole organism as broadly claimed.

The specification teaches by way of example sodium salicylate, BRL (after pre-treatment) and PGJ2 (after pre-treatment) in 3T3-L1 adipocytes reduces TNF-alpha induced lipolysis (where ERK1 / 2 activation is increased), the MAP kinase inhibitor PD98059 reduces TNF-alpha induced lipolysis in human cells in cell culture, and in contrast, the p38 kinase inhibitor SB203580 stimulates TNF-alpha induced lipolysis. The specification teaches only prophetically design of other ERK1/2, MEK or JNK inhibitors. Although there are some general MAPK

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inhibitors known in the art, neither the specification nor the art teach design of specific inhibitors which would have the claimed functions *in vivo*. The examples of inhibitors taught by the specification for use in cells in culture for reduction of lipolysis in cell culture cells induced in a particular way, do not correlate broadly to any possible inhibitor of any ERK1/2, MEK or JNK composition for the functions claimed in any whole organism.

There is a high level of unpredictability that the inhibitors taught in the specification as filed would function in a whole organism as claimed. One of the inhibitors taught in the specification as filed, PD098059, was shown to have no effect on noradrenaline-stimulated lipolysis as taught by Fryer et al. Thus, depending on the mechanism of stimulation of lipolysis, there is variability in the ability of known MAPK inhibitors to function to decrease lipolysis. Further, such known inhibitors are generally not specific for any one component of the MAPK pathway and are known to have many possible physiological changes in a whole organism. The other inhibitors taught in the specification were pre-administered to the cells in culture prior to stimulation of lipolysis by TNF-alpha. For these examples, there is no established correlation between administration of any possible inhibitor to cells in cell culture and administration to whole organisms as broadly claimed. Especially in the instant case of pre-treated cells, there is not a direct correlation to any complex disorder such as lipolysis, where an unknown number of variables are acting on causing the disorder (lipolysis can be caused by many different causes having different pathologies), for one skilled in the art to expect a treatment effect from looking at the effects of pre-treated cell culture cells. Although several key components of MAPK

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pathways are known, such as ERK1/2, MEK and JNK, the downstream effects of modulation of any known member of any MAPK pathway in any whole organism for treatment of lipolysis was not predictable at the time the invention was made. Specifically, since neither the specification nor the art teach inhibition of a specific component of a MAPK pathway having correlation to a direct reduction of a specific lipolysis condition in a whole organism, one skilled in the art would not have been able to practice the methods of prevention or treatment broadly claimed for prevention or treatment of any lipolysis related disease in any whole organism with any inhibitor of ERK1/2, MEK or JNK.

In regards to design of antisense, ribozyme or other gene inhibitors for instance, there is a further high level of unpredictability for design of such inhibitors which target a gene and function in a whole organism for treatment purposes as instantly claimed. Note the following unpredictability in the art for antisense and related ribozyme and triplex arts:

The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in

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vivo) are not distributed and internalized equally among organs and tissues.... Unfortunately, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2).”

In vitro, antisense specificity to its target may be manipulated by “raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments.” (Branch, p. 48) Discovery of antisense molecules with “enhanced specificity” *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo*: it “is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49).”

One of skill in the art would not accept on its face the successful delivery of any antisense designed to a known gene *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly

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unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require *de novo* “trial and error” experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

6. Applicant's arguments filed 3/4/02 have been fully considered but they are not persuasive.

Applicants response is found on pages 5-9 of the amendment filed 3/4/02.

Applicant states that “the specification demonstrates that PD098059 inhibits RNF-alpha-induced lipolysis. In addition, Applicant demonstrated that ERK1/2 inhibitors also inhibit basal lipolysis (see, e.g., specification at page 62, lines 3-6 and Applicant's publication Zhang et al. (2001) Scientific Sessions, Diabetes, A13:49-OR, attached hereto as Exhibit I). Applicant has also demonstrated that PD098059 blocks catecholamine-, forskilin-, and CL316,243-, a beta-3 agonist, stimulated lipolysis by 50% (see Applicant's publication Shen et al. (2001) Scientific Sessions, Diabetes, A13:51-O, attached hereto as Exhibit II).” Applicant further states that “[r]egarding Fryer et al., this reference does not show that noradrenaline-stimulated lipolysis is not inhibited by PD098059. The paragraph discussing the effect of PD098059 is at page 516, second paragraph under “Signaling mechanisms for insulin's action on lipolysis.” In this paragraph, the authors state that they examined whether there was any involvement of the MAP kinase pathway in the antilipolytic effect of insulin. The authors conclude that “PD098059 had

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no effect to impair effect of PD098059 on insulin's inhibition of lipolysis is also evidenced by Fig. 4 at page 518, treated with noradrenaline only. Thus, since insulin inhibits noradrenalin-stimulated lipolysis, the effect of PD098059 on cells treated with noradrenaline and insulin would be hidden by the effect of insulin. Thus, Fryer et al. Do not teach that PD098059 does not inhibit noradrenalin-stimulated lipolysis. Thus, contrary to the Examiner's statement, there is no variability in the ability of known MAPK inhibitors to function to decrease lipolysis."

However, it is not clear how applicant comes to the conclusion that "there is not variability in the ability of known MAPK inhibitors to function to decrease lipolysis" since the function of insulin in a subject *in vivo* would surely be a critical factor in the effects of the PD098059 addressed above for use in the instantly claimed methods. Applicant states on one hand that PD098059 would work in a whole organism to decrease lipolysis, but on the other hand states that in the presence of insulin it would not be detection. Since all whole organism mammals, such as humans, have insulin regulation in cells *in vivo*, one of skill in the art would not know how to use the PD098059 in cells *in vivo* if insulin masks the effect of the PD098059. Furthermore, the abstracts provided in Exhibits I and II, applicants own work, do not further provide a teaching of use of any specific ERK 1/2, MEK or JNK inhibitors in cells in a whole organism for the claimed effects on prevention or treatment of lipolysis related disorders.

Applicants further state that "PD098059 is known to inhibit MEK1, which is an activator of ERK1/2 (see, e.g., page 60, lines 4-5, of the specification). In addition, this inhibitor is highly selective, and does not appreciably inhibit the following kinases at 50 micromolar concentration:

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MAP kinase; protein kinase C, v-Src; EGFR tyrosine kinase; NGFR (trk-A) tyrosine kinase; PDGFRbeta tyrosine kinase; PI-3 kinase; E. Coli histidine kinase NRII; and Raf (see col. 9, lines 31-40 of US. Patent 5,525,625, attached hereto as Exhibit III; wherein PD098059 is referred to as 2'-amino-3'-methoxyflavone). It also shows selectivity between biological activities, e.g., between the mitogenic and metabolic effects of insulin (see, col. 8, lines 60-61 of U.S. patent 5,525,625). Similarly, another MEK inhibitor, U0126, described in Favata et al. (1998) J. Biol. Chem. 273:18623 (attached hereto as Exhibit Iv), shows a high selectivity towards MEK1 and MEK2. It does not significantly inhibit any of the following kinases: protein kinase C., Abl, Raf, MEKK, ERK, JNK, MKK3, MKK6, Cdk2 and Cdk4 (Favata et al., *supra*). Thus, contrary to the Examiner's assertion, inhibitors of the MAPK pathway can be specific for any one component of the MPAK pathway."

In response, the predominant issue for the instant claims is the lack of ability to make and use the broad scope of inhibitors claimed for prevention or treatment of any disease affiliated with lipolysis or elevated FFA levels in any subject. The data provided by application on the selectivity of PD098059 and U0126 to inhibit MEK is not provided in an *in vivo* context which is critical to the claimed invention. Part of the instant rejection centers on the ability of one of skill in the art to make any inhibitor of the MEK, JNK or ERK1/2 genes or proteins. As argued above, there is a high level of unpredictability to make inhibitors such as the claimed antisense or ribozymes for use in a whole organism due to the unpredictable factors in the art for finding a correlation between use in a cell in cell culture and use *in vivo*. Part of the instant rejection

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centers on the ability of one of skill in the art to use any possible inhibitor to any MEK, JNK or ERK1/2 in a subject for the claimed functions, reducing lipolysis. The data provided above for PD098059 and U0126 does not teach how to make and use any other type of inhibitor to MEK, JNK or ERK1/2. Nor do those results show how to use those compounds for the instantly claimed methods of prevention or treatment of any possible disease as broadly claimed.

Applicants further state that “at least one member of the MAPK pathway is the target of a drug that is in Phase II clinical trials. The inhibitor is an antisense molecule targeted to Raf (which activates MEK) that is produced by ISIS Pharmaceuticals, Inc. (ISIS 5132). Even if some inhibitors may have undesirable physiological changes in a whole organism, the specification teaches how to conduct *in vitro* and *in vivo* tests to determine undesirable physiological changes. For example, *in vitro* assays for determining the effect of a compound on lipolysis are described, e.g., in the Examples and at pages 38 and 39 of the specification. These assays would reveal whether an inhibitor has undesirable properties. In addition, the specification teaches, e.g., at page 49, lines 13-22, various animal models, well known in the art, which can be used to test MAPK pathway inhibitors without undue experimentation. Such animal models would reveal the existence of undesirable physiological changes in a whole organism. Clinical trials would reveal the existence of undesirable physiological changes in a whole organism. Applicant notes that there is no requirement that clinical trials be conducted for patentability. In addition, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. M.P.E.P. 2164.08(b). As indicated above, a person of skill could determine

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which embodiments would be inoperative or operative with expenditure of no more effort that is normally required in the art. Thus, the claims are enabled.”

In response, the factors listed in MPEP 2164.01(a) were weighed in the determination of the lack of enablement of the instant claims. Primarily, due to the high level of unpredictability in the art of drug development, such as the art of antisense (see also MPEP 2164.06(b)(A)), and the lack of specific guidance in the specification as filed for making clearly operable embodiments of the claimed inhibitors for the claimed uses *in vivo*, one of skill in the art would have necessarily practiced undue experimentation to make and use the invention as broadly claimed to overcome the unpredictable factors argued above. Note also that MPEP 2164.08(b) states that “claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.” (emphasis added)

Applicant further states that “Applicant has demonstrated that pretreatment of cells with MAPK inhibitors results in inhibition of lipolysis. Thus, treatment of a whole organism with MAPK inhibitors would at least prevent the appearance of lipolysis in cells that have been contacted with the MAPK inhibitor prior to being contacted with the agent inducing lipolysis. Thus, contrary to the Examiner’s statement, a person of skill in the art would expect a treatment effect from looking at the effects of pre-treated cell culture cells. Furthermore, as indicated in the

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attached Declaration under 37 C.F.R. 1.132 by Andy S. Greenburg, MAPK pathway inhibitors also inhibit lipolysis in the absence of pretreatment.”

In response, as pointed out above, the examples in cells in cell culture do not provide a clear picture of how the MEK inhibitors taught in the specification would function in cells in a whole organism. Analogous to the unpredictability in the antisense art, is the ability to target the desired cell(s), and provide a sufficient concentration of the therapeutic agent in order to effect the claimed functions. Since the claims are broadly drawn to any disease, and prevention of any disease as well as treatment, the specification as filed has not provided clearly what the operative embodiments are for such broad use. Absent such a clear presentation, one of skill in the art would not understand how to make and use the breadth of the claimed invention. Furthermore, applicants’ arguments are directed broadly to any MAPK inhibitor, and do not address the issues in the current claims drawn to inhibition of JNK, ERK1/2 or MEK genes or proteins *in vivo*. Since not all cells have the same pathways, the guidance in the art and specification at the time the invention was made would need to address the inhibition of these targets in specific cells or tissues and further, the nexus or correlation between inhibition of these targets and a particular disease state. Absent such guidance, one of skill in the art would necessarily practice de novo research to determine all of these significant and integral relationships *in vivo*.

Applicants state that “there is a reasonable correlation between the claimed therapeutic methods and the *in vitro* examples provided in the specification, that is, the claimed methods would be convincing to a person of skill in the art based on the *in vitro* results. A person of skill

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in the art would be without basis to reasonably doubt Applicant's asserted utility on its face. The Examiner has not provided any evidence to the contrary, and has not satisfied its initial burden. Applicant has demonstrated that several inhibitors of MAPK pathways reduce lipolysis of cells *in vitro*. Applicant has also demonstrated that the activity of ERK1/2 is inhibited in adipocytes by the MAPK pathway inhibitor used (see, e.g., Figs. 3, 6A and 7A-C). Accordingly, the claimed methods would be credible to a person of skill in the art."

Applicant states that "[t]o further substantiate any doubt as to the asserted utility, the Applicant has shown that inhibition of the MAPK pathway in fresh human adipocytes results in inhibition of basal and TNF-alpha induced lipolysis (see attached Declaration Under 37 C.F. R. 1.132 by Andrew S. Greenburg). As further described in the Declaration, the Applicant has also demonstrated that another inhibitor, U0126 (Favata et al., *supra*), which is a stronger inhibitor than PD098059, inhibits basal and TNF-alpha induced lipolysis in fresh human adipocytes to a higher extent than PD098059. Also, the Applicant has demonstrated inhibition of lipolysis with a recombinant adenoviral vector encoding a dominant negative Erk-1 (see attached Declaration). The Declaration does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed...."

In response, the above rejection is based on the fact that the claims are drawn to prevention and/or treatment of any possible disease in any possible whole organism subject, and is not drawn to reducing lipolysis in cells in cell culture. The argument above is that there is a high level of unpredictability in the art that one of skill in the art would be able to accomplish the

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invention as claimed. Since the claims are so broadly drawn to prevention and treatment of any disease practically, then as MPEP 2164.08(b) states, the specification as filed must provide clearly what the operative embodiments of the claimed invention are or would be. For one class of the claimed inhibitors, the antisense molecules, there is a high level of unpredictability in the art and it is clearly set forth above that no guidance clearly exists in the art for making and using antisense to a target gene *in vivo* due to the lack of correlation in the art between use of antisense in cells in cell culture and *in vivo*. Correlations can be easily drawn to other types of yet undiscovered compounds that could potentially bind JNK, ERK1/2 or MEK genes or proteins because the same issues exist for a high level of unpredictability in the art for delivery and therapeutic effect *in vivo* due to the environment of a whole organism versus a cell in cell culture.

Although Dr. Greenburg shows the effects of PD098059 and U0126 in fresh adipocytes, the claims are not limited to reducing lipolysis in adipocytes, but are drawn to methods of prevention and treatment of any disease associated with lipolysis. Thus, there is a whole set of relationships between showing effects on fresh adipocytes in cells in cell culture from healthy subjects and showing effects *in vivo* after administration of these compounds for treatment or prevention of any disease associated with lipolysis. Presumably, cells having lipolysis related disorders do not function equivalently to cells which undergo normal (healthy) regulation of lipolysis, and thus, the set of circumstances in the diseased cells would be entirely different from the set of circumstances in a normal, healthy cell *in vivo*. Furthermore, a major problem with treatment and especially prevention of any such disease *in vivo* arises from the fact that one of

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skill in the art must know how to contact the desired cells or cell tissues in vivo to the extent that the therapeutic or preventative effect is demonstrated. From the antisense articles cited above, it is clear that not all tissues in vivo are easily accessible to treatment with antisense, and further, that there is a fine line between delivery of enough of the antisense for effective down-regulation of the gene, and delivery of a toxic amount of the antisense, which must be determined on an antisense-by-antisense basis.

Applicant points to portions of the Branch reference which teach that some antisense are in clinical trials. However, as stated above, each antisense for use in vivo, must be evaluated for its desired treatment effects on a case-by-case basis since there is no uniform guidance in the art for making and delivering any antisense since treatment of different genes requires different approaches. Just as applicant notes that "solid tumors are not the target site in the claimed method" applicant does not clarify in the claimed invention what the target site(s) are for the instantly claimed inhibitors. Applicant states that "[t]hus, even if certain oligonucleotides may not be distributed and internalized equally among organs and tissues, the cited references provide no evidence that antisense molecules would not reach and enter target cells in the claimed treatment." Applicant further states that "numerous antisense and ribozyme products are currently in clinical trials or have been approved.... Thus, one skilled in the art would be able to make and use the claimed invention using the application as a guide. Applicant notes that the evidence provided by Applicant need not be conclusive, but merely convincing to one skilled in the art. M.P.E.P. 2164.05."

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In response, the ability to use an antisense to a gene target not claimed in the instant claims or useful for prevention or treatment of a disease associated with lipolysis, are not relevant to the instant claims. Yes, individual antisense therapeutics are available for use *in vivo* for specific gene targets, but not to the instantly claimed gene targets for the instantly claimed uses.

B. Claims 15-17 are drawn to methods for determining whether a subject has or is likely to develop a disease or condition caused, or contributed to, by lipolysis, comprising determining the activity of an ERK ½ and/or JNK in the individual, and wherein an abnormally high ERK ½ and/or JNK activity indicates that the individual has or is likely to develop a disease or condition caused, or contributed to, by lipolysis. Claim 16 specifies wherein determining the activity of an ERK ½ and/or JNK comprises determining the ERK ½ and/or JNK protein level, and wherein an abnormally high ERK1/2 and/or JNK protein level is an abnormally high ERK1/2 and/or JNK activity. Claim 17 specifies that the determining the activity of an ERK1/2 and/or JNK comprises determining whether the ERK1/2 and/or JNK protein is a mutated ERK ½ and/or JNK protein.

The specification teaches by way of example sodium salicylate, BRL (after pre-treatment) and PGJ2 (after pre-treatment) in 3T3-L1 adipocytes reduces TNF-alpha induced lipolysis (where ERK1 / 2 activation is increased), the MAP kinase inhibitor PD98059 reduces TNF-alpha induced lipolysis in human cells in cell culture, and in contrast, the p38 kinase inhibitor

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SB203580 stimulates TNF-alpha induced lipolysis. The specification teaches only prophetically design of other ERK1/2, MEK or JNK inhibitors. Although there are some general MAPK inhibitors known in the art, neither the specification nor the art teach design of specific inhibitors which would have the claimed functions *in vivo*. The specification does not further provide a direct and clear correlation between the inhibition of ERK 1/2 or JNK and the ability to predict a disease state involving lipolysis from said data.

Neither the specification nor the prior art taught at the time of filing what a "abnormal" level of either ERK 1/2 or JNK gene or protein is, or what mutation in the protein are indicative of any disease associated with or contributed by lipolysis. The unpredictable factors thus are the basal levels of these genes or proteins, and in what cells or tissues they are measured in, and in what whole organism subject, since neither the specification nor the prior art provides this information. Absent this information, one of skill in the art would not be able to practice the claimed methods since the relative expression levels between "normal" and "abnormal" or regular and mutant where not established. For instance, it is unpredictable what the expression levels are from between species or individual subjects, and thus it is unpredictable what the expression in a disease state is representative of. Kinases are ubiquitous proteins and are present in highly fluctuating amounts in cells and are not temporally or spatially preserved such that there is a known about of ERK 1/2 or JNK which is considered "abnormal". As such, one of skill in the art would necessarily practice "trial and error" *de novo* experimentation to make and use the claimed invention. Since the determination of the effect of any possible disease relative to ERK

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½ or JNK levels was not taught in either the specification as filed or the prior art, one of skill in the art would not have sufficient guidance to overcome the unpredictability in this determination, and thus would necessarily practice an undue amount of experimentation.

Allowable Subject Matter

7. Claim 18 is allowable. Claim 18 is drawn to a drug screening method for identifying a compound which reduces TNF-alpha induced lipolysis comprising: (I) isolating a compound which is an ERK ½ and/or JNK inhibitor; (ii) contacting an adipocyte with the compound of step (I) and TNF-alpha and determining the level of lipolysis, wherein a lower level of lipolysis in the presence of the compound of step (I) relative to the level of lipolysis in the absence of the compound of step (I) indicates that the compound reduces lipolysis, to thereby identify a compound which reduces lipolysis.

The closest prior art, such as Klein et al. (U.S. Patent 6,25,059) and Momose et al. (U.S. Patent 6,110,948) do not specifically teach nor fairly suggest the screening of ERK ½ or JNK inhibitors in adipocyte cells for determining the level of lipolysis as instantly claimed.

8. Claims 1-17 and 19-28 are further considered free of the prior art since the prior art did not teach nor fairly suggest the use of ERK ½, JNK or MEK inhibitors for prediction or treatment of any disease associated with lipolysis.

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9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.



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M. M. Schmidt
April 7, 2003